Poster Session 2 – Pharmaceutical Technology

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Raman spectroscopy as a tool for preliminary drug testing on human cells

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We have developed a novel biophotonics technique using Raman spectroscopy to monitor the interaction of chemicals with cells non-invasively and in-situ over a period of days. As an illustration of the potential of the technique, the well-documented chemical etoposide is used. Etoposide is a type II topoisomerase, used as an anti-cancer drug and known to induce single- and double-stranded breaks in the DNA which our technique can confirm. Human lung adenocarcinoma cells (A549) were used throughout these experiments. The cells were seeded onto an MgF_2 substrate for Raman analysis. The substrate is ideal as it has a low signal in the area of biological importance and has a low solubility so does not affect the behaviour of the cells. During the analysis the cells were kept in culture medium at 37°C. The Raman spectra were taken in multiple locations in the cell in around 6 min, n = 30 cells/test. This amount of high-power 785 nm laser has been shown not to induce any damage to the cells. A classical least squares (CLS) model of the cell was constructed to determine biochemical changes induced by etoposide. The CLS basis spectra were obtained by using commercially available representative chemicals such as DNA, RNA, alpha and beta proteins, lipids, carbohydrates and phospholipids. In this method, a spectrum is approximately equivalent to the linear combination of the basis spectra so any changes that occur in the relative amounts of these components can be monitored over time. No changes were observed in the concentrations of the components except for DNA that decreased by approximately 40% after 24 h and 50% after 48 h compared with controls. There is known to be a balance between pro and anti-apoptotic proteins within a cell and although this balance has changed, total protein levels remained constant. Following etoposide treatment western blotting revealed an increase in p53 due to DNA fragmentation, while cell morphology (monitored by a Leica microscope connected to the Raman spectrometer) became rounded. Conventional, invasive cell viability tests were performed using the WST-1 and MTT to compare with the Raman results. Viability decreased by 30% after 24 h and 60% after 48 h exposure to etoposide compared with untreated controls. This is due to DNA fragmentation that causes the cells to enter an apoptotic pathway. Raman spectroscopy can thus model cellular changes in real-time. The potential to analyse any cellular component makes the technique a powerful drug screening technology. We propose that our biophotonics cell monitoring system can speed up pharmaceutical R&D by rapidly eliminating drug candidates that are deleterious to human cells. This may eventually offer a viable alternative to some forms of animal testing. We are presently working on enhancing the CLS model to incorporate many more cellular components and analysing other cellular changes with a high degree of reproducibility.

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The influence of wet granulation on the mucoadhesive properties of HPMC and NaCMC containing tablets

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The use of mucoadhesive drug delivery systems for systemic or local administration of various therapeutic drugs, including proteins and peptides, has attracted a great deal of interest in recent years (Hass & Lehr 2002). Wet granulation is a popular method used in tablet preparation. In this study the influence of this technique on the mucoadhesive properties of tablets prepared from the cellulose derivatives, HPMC and NaCMC, was investigated. For the purpose of this study 100 mg flat-faced tablets with a diameter of 9 mm were prepared by compression, using a single punch tablet machine. Each tablet contained 40% spray-dried lactose as diluent, and a 5% PVP aqueous solution was used as the granulating agent. Various HPMC/NaCMC physical mixtures were prepared by thorough mixing and granulated with the PVP solution. The HPMC/NaCMC mixtures were either partially or completely granulated. Next, granules were uniformly mixed with lactose (and the remaining HPMC/NaCMC powder not granulated) and compressed into tablets. For the purpose of comparison, directly compressed (DC) tablets were also prepared. Tablets prepared were examined in terms of their in-vitro mucoadhesive strength and duration of mucoadhesion, based on the methods used in a previous study (Mortazavi 2002). In here tablets were placed in contact with rat intestinal mucosa (model membrane) within a pH 6.8 phosphate buffer solution at 37°C. Results showed that tablets prepared by completely granulating the HPMC/NaCMC mixtures had lower mucoadhesive strengths than their corresponding formulations, which were partially granulated, or those prepared by DC. However, the duration of mucoadhesion (maximum time tablet remained in contact with the mucosal surface under a constant tensile force) of tablets was found to improve by granulation. Increasing the concentration of extra-granular NaCMC helped to increase the mucoadhesive strength of the resulting tablets, although the duration of mucoadhesion of the test tablet was reduced. In contrast, increasing the amount of HPMC in the tablet, and in particular within the granules, resulted in an increased duration of mucoadhesion, despite lowering the mucoadhesive strength of the formulation. As expected, the process of wet granulation, especially by incorporating the HPMC/NaCMC mixture completely within the granules, managed to improve the flowability and compressibility of the powder mixture, as well as increasing the tablet hardness. Overall, an HPMC/NaCMC mixture at a ratio of 1:3, in which 60% was granulated and the remaining 40% kept in the powder form and added extra-granularly, was found to produce the most reasonable mucoadhesive strength and duration of mucoadhesion, in-vitro. This formulation also had a suitable appearance and an appropriate hardness. In conclusion, the process of wet granulation appears to influence the mucoadhesive properties of HPMC/NaCMC-containing tablets, presumably as a result of altering the amount of immediately available polymer for interaction with the mucosal surface, as well as the extent of water uptake and overhydration of the tablet. This finding should be carefully considered in the formulation of a putative mucoadhesive drug delivery system, capable of remaining in place for a reasonable period of time.

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The effect of drum surface texture in dynamic avalanching of powders

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A material with good flowability is generally described as possessing the ability to move freely in a consistent and reproducible manner as individual particles not requiring external assistance (Carr 1965). An efficient measurement of material flowability could provide a useful tool for the selection of excipients, development methods and equipment during formulation development. (Presscott & Barnum 2001). Materials placed in a rotating drum of the Aeroflow generate a pattern of movements due to their characteristic surface instability. These spatial structures form a unique fractal fingerprint in relation to time, which is electronically recorded. This study evaluates the influence of the drum surface texture of the Aeroflow on the flow patterns obtained and on particle size distribution. The dynamic flow properties of three granules made by dry granulation using a (Fitzpatrick chilsonator model IR520) were tested. The granules comprised of adipic acid, fast-flow lactose, hypromellose, anhydrous calcium phosphate and magnesium stearate. The granule batches will be referred to as G0042, G1042 and G2042. The drum operates within the range of 40–200 s/rev. Average times between avalanches (MTA) values were obtained. Tests were carried out on a smooth surface (SS) and perforated metal collar surface (MCS). Further tests were carried out on granule batch G0710062 using smooth masking tape, curved masking tape and the perforated metal collar.

Slipping flow behaviour, lower MTA values and percentages of fines were observed for samples tested with the smooth surfaces (Table 1). The metal collar surface showed a higher occurrence of avalanching and values of MTA with the same granules. Sieve analysis on tested samples showed a higher percentage of fines for granules tested with the metal collar. The samples tested with the curved masking tape showed more avalanching (17%) compared with the smooth surface and 2.21% less avalanching than samples tested on the perforated metal collar with no evidence of granule abrasion. The use of an appropriate inner surface in the Aeroflow drum prevents the occurrence of granule abrasion caused by very rough surfaces. The predominant slipping flow pattern induced by a smooth surface may result in a low MTA. Flow patterns characteristic of the material properties are required for an accurate assessment of flowability. Optimising the surface texture of the drum enables dynamic movements that are linked directly to the material flow properties.

Table 1 MTA and % of fines for granules tested at 120 s/rev

Batch	SS (MTA)	MCS (MTA)	% Fines SS	% Fines MCS
0042	2.7 ± 0.07	4.17 ± 0.13	1.34 ± 0.07	1.56 ± 0.79
1042	3.34 ± 0.36	3.65 ± 0.08	0.22 ± 0.14	0.39 ± 0.29
2042	3.56 ± 0.16	3.89 ± 0.43	0.12 ± 0.19	0.37 ± 0.31

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Fabrication of gastroretentive metformin hydrochloride tablets: application of optimised viscosity approach

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The aim of this investigation is to stress the need for development of gastroretentive sustained release formulations of metformin hydrochloride (GRMHs). The absorption window of metformin hydrochloride (MHCl) is essentially in the upper part of small intestine and it has poor colonic absorption (Marathe & Wen 2000). Moreover, it has also been reported that GRMHs have demonstrated better bioavailability than immediate release formulations. Study of currently available market formulations of sustained release MHCl tablets lacked gastroretentivity. Thus, an attempt was made to formulate GRMH using hydrophilic polymers. The formulations comprised of gel forming polymer (HPMC K4 M and/or HPMC K100 M) or polymer blends and gas generating agents (sodium bicarbonate and citric acid). The polymers demonstrated significant effect on drug dissolution profile. Hence, apparent viscosity approach was applied to carry out systematic study. The theoretical calculation of apparent viscosity of polymer and polymer blends was carried out using equation given by Khanvilkar et al (2002).

The GRMH tablets (batches A1 to A9) were prepared using polymer/polymer blends as shown in Table 1. The tablets were subjected to in-vitro dissolution studies in 0.1 N HCl and kinetic modelling of the data was carried out. All the batches followed the Korsemeyer & Peppas model for drug release, which was used for the calculation of time required to release 25% drug (t25) and time required to release 50% drug (t50). Results of linear regression analysis between t25/t50 and theoretical apparent viscosity revealed good correlation. The generated equations were used for calculation of optimum apparent viscosity. Theoretical t25 and t50 was calculated from theoretical dissolution profile obtained using pharmacokinetic data of MHCl. Results of theoretical t25 and t50 were used for the calculation of optimum apparent viscosity of the polymer blend (~66633 cps). On the basis of the above calculation, batch A10 was prepared, which was deemed to have dissolution profile similar to theoretical dissolution profile. The similarity factor f2 was applied to adjudge the similarity between the two dissolution profiles. Table 2 indicates the similarity between two dissolution profiles. Thus, the optimized viscosity approach proved to be an important tool in the fabrication of GRMH, having drug release characteristics similar to the theoretical dissolution profile.

Table 1 Characteristics of GRMH tablets

Batch no.	Amount of HPMC K4 M (mg)	Amount of HPMC K100 M (mg)	Theoretical apparent viscosity (cps)	t25 (min.)	t50 (min.)
A1	250	0	4000.00	29.88	143.98
A2	200	50	8516.52	19.98	123.17
A3	175	75	12 117.82	30.63	153.07
A4	150	100	16 987.10	31.60	155.96
A5	125	125	23 489.30	50.40	189.05
A6	100	150	32 073.06	54.59	195.98
A7	75	175	43 285.33	73.63	249.02
A8	50	200	57 788.01	80.76	237.14
A9	0	250	100 000.00	96.56	300.74

Table 2 Dissolution profile of batch A10

	A10	Theoretical dissolution profile
t25 (min)	73	79
t50 (min)	246	255
f2	81.94	

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Comparative rheological study of cephalexine oral suspensions

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Despite the production of oral suspensions in pharmaceutical companies, several shortcoming and problems exist in the formulations, among which are the caking phenomena, proper instability and lack of optimal disperse system upon consumption. The significance of these complications leads us to the rheological behaviour study in the formulation of said suspension as well as their quantity and quality tests. This study was carried out to imply the various types of rheological tests against the domestic oral suspensions of cephalexine 125 mg/5 mL and 250 mg/5 mL and on its standard samples (i.e. Ospexine) as well. To find out the non-Newton rheological behaviour of those suspensions, measuring apparatus of capillary viscometers and Cone-Plate rheometer were used. The rheological features of the domestic oral cephalexine and its standard products were comparatively assessed using manual and automatic settings of a cone-plate rheometer. Meanwhile, the idea of replacing of the capillary viscometers with cone-plate rheometer for viscosity measuring of those suspensions were tested by evaluation and interpretation of non-newtonian rheological data obtained from both apparatus. The viscosity/time rheograms of domestic samples of 125 mg/5 mL and 250 mg 5 mL at 50 rev min^{-1}, showed rheopectic behaviour whereby they demonstrated inter and intra-batches variation when the viscosity rate was increased. Evaluation of such data obtained from the standard samples also demonstrated the same behaviour, except that the 125 mg/5 mL samples showed higher viscosity than 250 mg/5 mL, especially during 20–45 min. Viscosity rheograms on the various shear rates showed inter-batch variations in the domestic 125 mg/5 ml samples, such that some batches were identified by dilatancy profile — which is the indicator of higher deflocculation of the system — whereas some others showed rheopectic behaviour. Meanwhile, both standard samples of 125 mg/5 mL and 250 mg/5 mL demonstrated rheopectic rheograms. The area under curve (AUC) for the standard sample of 125 mg/5 mL was bigger than the 250 mg/5 mL, indicating a higher degree of anti-tixotropy of 125 mg/5 mL than for the 250 mg/5 mL, whereas both domestic samples demonstrated the same degree of anti-tixotropy. The comparative studies of viscosity obtained from both capillary viscosometers and cone-plate rheometer in different shearing rates showed different viscosity in the same speed and existing a non-linear correlation between two apparatus indicating that there was no definite equilibrium for each product in every concentration. This indicates that testing of one product in a certain concentration can probably lead to a predictable proportion between their viscosities enabling us to predict one by knowing the other.

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Low frequency dielectric relaxation study on hydrated sucrose lyophiles

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The stability of most lyophilised pharmaceuticals is dependent to a large extent on the residual moisture content (Rey & May 1999). A general approach for predicting stability may be established on the basis of molecular dynamics measurement by either thermal, mechanical or dielectric relaxation. Of these,

dielectric relaxation spectroscopy (DRS) offers the opportunity to investigate the properties of water via the study of protonic charge percolation. This study aims to investigate proton charge percolation in hydrated sucrose lyophiles with a view to establishing the sensitivity of the technique at low moisture contents (< 3%). Samples of sucrose lyophiles were dried to constant mass (~0% moisture) over phosphorous pentoxide. These samples were re-hydrated to give moisture contents up to 3% by subjecting to 26–32% RH. The frequency dependence of the dielectric properties of the samples (~0.22 g) sandwiched between two stainless steel plate electrodes (25 mm diameter and 1 mm separation) were analysed between 0.1 and 10^6 Hz, using a Solartron 1255/1296 impedance analyser. Two distinct processes, at low and intermediate frequency, were observed for all samples. The low frequency response (< 1 Hz) was shown to follow the fractional power law $\varepsilon^*(\omega) = A(i\omega)^{-P}$. This low frequency response was attributed to the quasi-dc percolation of protons through the sugar matrix which are presumed to originate from the water within the hydration surface of the amorphous matrix, as well as from the sugar matrix itself (Dissado & Hill 1984). The increase in the pre-exponent A was observed, with increase in moisture content and is consistent with an increase in the size and/or number of clusters (Table 1). The exponent P showed a peak at 1% moisture, possibly due to a transition in structure and/or size of the hydrogen-bonded clusters of water molecules (Table 1). The other small weak relaxation process observed at intermediate frequency (centred at 1 kHz) is assumed to be due to the presence of grain boundaries within the sample, which truncate the paths of the otherwise mobile charge carriers, and thereby lead to localised induced dipole moments. The relaxation strength of the intermediate frequency process increased with moisture content, which is again consistent with an increase in the size and/or number of clusters. The relaxation time and distribution function α both decreased with increased moisture content as expected. The variation in the magnitudes of the exponent P, pre-exponent A, relaxation strength and distribution function α, with moisture content underline the sensitivity of DRS to the properties of the hydration surface, and structure, of lyophiles which might prove useful for predicting the stability of moisture-sensitive products.

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Table 1 The change in exponent P and pre-exponent A with moisture content

	Sucrose 1			Sucrose 2		
% H_2O	0.00	0.98	2.01	0.00	0.96	2.05
P	0.84	0.86	0.85	0.85	0.91	0.88
A	0.11	0.24	0.40	0.06	0.11	0.16

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Development of a micronutrient minibag for parenteral nutrition (PN) patients

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Micronutrients make up one of the component groups in PN formulations. Parameters that affect micronutrient stability have been previously outlined (Allwood 1994), with vitamins generally not considered to be stable for prolonged storage in PN formulations and therefore are not included in PN admixtures. This project has been undertaken to look into the possible development of a minibag preparation that would be especially useful to home PN patients who currently have to add their required vitamins at home just before infusion of the PN admixture. This initial study aims to look into the physical-chemical stability of an aqueous multivitamin formulation when stored under various storage conditions. Reconstituted multivitamin vials of Solivito N (Fresenius Kabi) were added to 100 mL of 0.9% sodium chloride in either glass bottles or Freeflex (Fresenius Kabi) bags. The solutions were stored in a pharmaceutical stability chamber (Sanyo Gallencamp PSC062) for one week at 25, 30 and 40°C at a relative humidity of 60% and exposed to light of intensity 0.7 klux, simulating hospital lighting conditions (Baker et al 1993). Similar test solutions were also tested under temperature-only conditions of 4°C. Samples were taken from all tests at 0, 3, 6, 24, 48, 72 and 168 h and stored at −80°C before HPLC analysis. Analyses for degradation of thiamine HCl, nicotinamide, pyridoxine HCl, folic acid (FA) and riboflavine sodium phosphate (RSP) were carried out using a validated stability-indicating reversed-phase HPLC method, content analysis of these samples at 0 h being regarded as the baseline content of 100%. Nicotinamide, pyridoxine HCl and thiamine HCl were found to be stable (more than 90% remaining) for one week under all temperature conditions tested, while FA and RSP in clear bags stored at 25°C were stable for 72 h; at 40°C in bags, RSP was only stable for 72 h. When exposed to light, nicotinamide remained stable; however pyridoxine HCl stability in solutions stored in clear glass at 40°C was reduced to 72 h, and for 24 h in clear Freeflex at 25, 30 and 40°C. Exposure to light reduced thiamine HCl stability to 72 h when stored in clear glass bottles at 25, 30 and 40°C, while the stability results for FA and RSP obtained with solutions exposed to light are presented in Table 1. In conclusion, nicotinamide was found to be the most stable of all the vitamins tested. Vitamins losses were least when solutions were stored with a light protective cover and kept refrigerated. These results are comparable with referenced data on individual vitamins (DeRitter 1982). Further tests with fat-soluble vitamins and trace elements are currently being carried out simulating real clinical setups.

Table 1 Stability (in hours) of FA and RSP, exposed to light

Vit	Container	25°C	30°C	40°C
FA	Clear G (FF)	72 (48)	168 (48)	168 (24)
	Dark G (FF)	168 (48)	168 (168)	48 (168)
RSP	Clear G (FF)	24 (6)	6 (6)	6 (3)
	Dark G (FF)	72 (72)	72 (72)	168 (168)

G = Glass, FF = Freeflex.

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A combined surface pressure-interfacial rheology study of the adsorption of polypeptides at air/liquid interfaces

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The full therapeutic potential of many peptide and protein drugs will not be realised until their specific delivery problems have been resolved. The pulmonary route, and specifically the lower alveolar airways, provides a very large surface area, a highly perfused vasculature and a more permeable mucosa than other routes. To develop delivery systems that will maximise the potential of this route, we have studied the adsorption of model polypeptide candidates at the air/liquid interface. Changes in the surface pressure and the interfacial viscoelastic properties were recorded simultaneously using a combined surface pressure-interfacial rheology approach. This approach consists of a Camtel CIR-100 interfacial rheometer using a NIMA Langmuir trough as the sample vessel. The trough area was held constant and polypeptide candidates were introduced to the phosphate buffer subphase (0.1 M, pH 7.4, 25°C), either below a clean surface or below a surface coated in a dipalmitoylphospatidylcholine (DPPC) monolayer. Measurements of the interfacial viscoelastic parameters (storage modulus, G′, and loss modulus, G″) and surface pressure (π) were then recorded against time using an oscillating De Noüy ring and a Wilhelmy plate, respectively. Two polypeptide candidates, differing in molecular weight, structure and isoelectric point, were chosen for these studies, namely lysozyme (14.5 kDa), and catalase (240 kDa). The effect of pH on the adsorption process was also investigated by altering the pH of the phosphate buffer subphase. The adsorption of polypeptides with a high molecular weight (i.e. catalase) to a clean air/liquid interface, resulted in an immediate, rapid increase in the values of π, G′ and G″, producing an elastic film at the interface. Lysozyme also produced elastic films at the interface, but the increases in π, G′ and G″ occurred after a period of ~10 min and were much less rapid. However, the rate of change in the values of π, G′ and G″ could be increased by altering the pH of the subphase so that it was closer to the isoelectric point of the polypeptide under investigation. DPPC formed a viscous monolayer when spread at the air/liquid interface. The introduction of catalase to the subphase beneath this monolayer resulted in an increase in the values of π, G′ and G″, and a change from a viscous (G″ > G′) to an elastic monolayer (G′ > G″).

However, no changes in the properties of the DPPC monolayer were observed for the small molecular weight lysozyme. The rate of polypeptide adsorption at the air/liquid interface is therefore greater for catalase, which can also induce structuring in DPPC monolayers, than for lysozyme. The adsorption rate is also markedly increased the closer the pH of the subphase is to the isoelectric point of the polypeptide.

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Investigation into the mechanism of cryoprotection of lactate dehydrogenase by Tween 20

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Non-ionic surfactants are used as cryoprotectants for protein molecules during freeze-drying although the mechanism by which they act is not fully understood. One proposed mechanism is that the cryoprotective effect is caused by the surfactant preventing adsorption of the protein onto the ice surface where it may denature (Chang et al 1996). In this case the cryoprotective effect of the surfactant should correlate with its critical micelle concentration (CMC). However, others have demonstrated cryoprotection at concentrations below the CMC (Nema & Avis 1993). An alternate hypothesis is that the non-ionic surfactant molecules bind to hydrophobic patches on the protein surface preventing denaturation and loss of activity. Isothermal titration calorimetry (ITC) is a highly sensitive technique that can determine binding enthalpies and stoichiometries and has been used previously to investigate the binding of surfactants to proteins (Bam et al 1998). The aims of this study were to ascertain whether binding occurred between Tween 20 and a model protein lactate dehydrogenase (LDH) and determine whether this binding is pertinent to understanding the mechanism by which Tween 20 protects LDH during freeze-thawing. All materials were obtained from Sigma. LDH type II from rabbit muscle in ammonium sulphate solution was dialysed and filtered. ITC experiments where performed using a Thermometric TAM 2277. Two sets of experiments were performed. In both cases 5-μL portions of a 3.6 mM Tween 20 solution in citrate buffer pH 6.5 were titrated into 900 μL of either the citrate buffer or into a 625 μg mL^{-1} LDH solution in citrate buffer. Freeze-thaw experiments were performed using LDH concentration of 29 μg mL^{-1} and varying Tween 20 concentrations (0–90 μM) in citrate buffer pH 6.5. The experiments were carried out in a Virtis Advantage freeze-dryer, using freeze-drying vials and a 1-mL fill. LDH concentration and activity were measured by UV spectroscopy. Tween 20 was found to protect LDH from the freezing stress at concentrations significantly below its CMC (59 μM). At 5 μM Tween 20, LDH activity retained following the freeze thaw cycle was $59 \pm 5\%$. This increased to $78 \pm 9\%$ at 20 μM and $88 \pm 3\%$ at 40 μM. Further increases in the concentration of Tween 20 up to the CMC resulted in only a small increase in cryoprotection with $91 \pm 4\%$ of activity retained at both 50 μM and at 59 μM. In addition Tween 20 was found to bind to LDH with an enthalpy of binding of 1.39 kJ mol^{-1} and a binding stoichiometry of 2.4:1. Significant cryoprotection of LDH by Tween 20 at concentrations well below the CMC (59 μM) was observed. This would not be expected if the sole effect of the surfactant was to prevent adsorption of the LDH to the ice surface by steric means. Additionally binding of Tween 20 to LDH has been observed in solution. The low binding enthalpy is characteristic of hydrophobic interactions suggesting that Tween 20 binds to hydrophobic patches on the protein surface. This could explain the cryoprotection of LDH by Tween 20 at concentrations below its CMC.

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A novel granular tablet film coating system

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The preparation of tablet film coating suspensions based on hydroxypropyl methylcellulose (HPMC) is usually a challenge. HPMC is a fine powder and has a tendency to form clumps in water. These clumps are variable in size dependent upon the skill of the operator adding the powder to the water. Even the presence of small clumps can give rise to gelatinous structures called fish-eyes, which are problematic in that they are capable of clogging spray guns. Many procedures have been presented to overcome this problem including: heating the water to 80°C, the use of an adductor tube or an in-line disperser and stirring the suspension for 12–16 h. An alternative approach that has enjoyed some success is to blend the HPMC powder with other excipient powders (for example pigments and plasticizers) to dilute the HPMC, thereby reducing the tendency of the material to form clumps. Although the preparation of such powder blends is beneficial, clumping problems are still evident. Additionally these products are of a dusty nature and flow poorly. A significant development is the granulation of the powder blend with water. In these systems HPMC (and other resins) may be blended with pigments, plasticizers and other ingredients (e.g. flavours) in a high intensity powder blender with chopper blades to produce an intimate and uniform powder. Following this process water is sprayed into the blender at high atomization for approximately 2 min. This action promotes the formation of granules, by adhering the HPMC particles together with the other ingredients present. The application of water is critical for the generation of granules and the utilization of a liquid plasticizer alone is not sufficient as it is incapable of causing solubilization of the resin. The granules produced in this manner are non-dusting, free-flowing and partially hydrolyzed, rendering the system easier to suspend in water without the formation of clumps. This approach can be applied to any coating formulation that contains HPMC or alternative water soluble polymers. Additionally, as these systems are used in an aqueous format, the addition of water to produce the granular blend does not introduce an ingredient change.

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Assessment of the quality of film-coated tablets produced using a vertical centrifugal coater

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The Vertical Centrifugal Coater (VCC, Diosna Dierks & Söhne GmbH) represents a new design in film coating equipment and is claimed by the manufacturer to considerably reduce coating times compared with conventional side-vented perforated pans. The VCC utilises centrifugal force generated by a vertically rotating perforated outer cone to cause the cores to rise towards the top of the cone where they are guided into a stationary inner perforated cone through which they fall. As they exit the bottom of the cone they pass a spray gun that sprays with an angle of 360°. Hot air passes through the coater, continuously drying the product. This study was carried out to assess the quality and intra- and inter-batch uniformity of film coats applied using a VCC. Five batches of 10 mm round, scored, normal convex tablets of average weight 304 mg were coated in a VCC-5 with an 8% w/w Opaglos 2 formulation (Colorcon Ltd), which contained FD&C Blue number 2/indigo carmine dye as a marker. The coating conditions were kept constant and sufficient coating suspension applied to each 4-kg batch to give a 3% w/w coat (based on uncoated tablet weight). The appearance of tablet samples taken after 15 min coating (nominal coat level 1.29% w/w) and at the end of the coating run (approximately 35 min) was assessed visually, by light microscope and using SEM. The amount of coat applied and the coating uniformity were determined by spectrophotometrically analysing the amount of the marker dye dissolved from ten coated tablets at both coat levels from each batch. Coat thickness was determined using SEM. Visual assessment of the tablets after the application of a 3% w/w coat indicated the quality of tablets from all coating runs was good, the tablets being glossy and even in colour. Examination of the coats using a light microscope (×40) and a SEM showed that the coating formulation droplets had spread and coalesced well and that there was minimal spray drying in the score marks. There was no evidence of film cracking, edge splitting, poor adhesion or bridging. A small incidence of very minor "picking" was detected (typically about 3% of tablets per batch). Analysis of the coat applied to the tablets indicated that the average coating efficiency values were 94.1% and 95.6% for coat levels of 1.29% w/w and 3.00% w/w, respectively. The average final coat level varied between 2.78% w/w and 2.92% w/w for the five batches coated, indicating good inter-batch reproducibility. Coefficient of variation values (%CV) for the applied coat on the tablets tested from each coating run ranged from 5.74 to 8.93 for the 1.29% w/w coat level and from 2.92 to 5.23 for the 3.00% w/w coat level. This indicates an improvement in coat uniformity as the coat level increases and good intra-batch variation for the final coated tablets. The mean film thickness ($n \geq 16$) for the coated batches ranged from 24.6 μm to 26.1 μm, providing further evidence of good inter-batch reproducibility.

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The influence of polymer swellability on the release properties of matrix tablets

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A range of swellable and non-swellable polymers have been used in the preparation of modified release matrix tablets. In this work, the release of a soluble and a poorly soluble model drug has been determined utilising polymers with different swelling properties, characterised by a 'swellability index'. These polymers were hydroxypropylmethylcellulose (HPMC), xanthan gum, hydroxypropyl-cellulose (HPC), and polymethacrylate. The aim of the work was to interrelate polymer content and swellability to drug solubility and release. Formulations consisting of diluent, modified release polymer and drug were prepared using high shear wet granulation. Granules were compressed into 300 mg compression weight tablets and dissolution testing was performed. Dissolution release profiles obtained for each formulation were compared. The swelling potential of the release agent (Table 1) directly influenced both the granulation process and drug release from the matrix tablet (Table 2). The swelling potential of the polymer was attributable to both its molecular weight and solubility; the greater the solubility and molecular weight, the greater the swelling potential. Xanthan gum had the higher swellability index. The release of the soluble drug was 20 times slower from the xanthan gum matrix than from the HPC (MF Pharm) matrix which contained 4 times more polymer content than the xanthan gum matrix. The release of the poorly soluble drug type was more than 40 times slower from the xanthan gum matrix than from the HPC matrix (Table 2). The greater the swelling potential of the polymer the greater the influence on modification of drug release. Polymethacrylate had the least swelling potential and was most suitable at modifying drug release of poorly soluble drug types. An increase in polymer content or the use of an insoluble drug, both influence granulation by requiring more granulating solution to reach granulation endpoint. For soluble drug types, drug release is controlled predominantly by erosion/dissolution of the tablet matrix. The greater the swellability of the polymer, the slower the erosion/dissolution of the matrix and consequently the slower the drug release. For poorly soluble drug types, drug release is controlled predominantly by drug diffusion. Less swellable polymers are therefore more capable of modifying drug release of poorly soluble drug types.

Table 1 Mean swellability index

Polymer	Mean swellability index
Xanthan gum (Xantural 75)	108.3%
HPMC (Methocel K4MCR)	55.6%
HPC (Klucel HXF Pharm)	38.1%
HPC (Klucel MF Pharm)	32.2%
Polymethacrylate (Eudragit NE30D/NE40D)	Limited swellability

Table 2 Effect of polymer type/content on drug release

Polymer	Polymer content	Insoluble drug (T90% h)	Soluble drug (T90% h)
Xanthan gum	5%	>24	11
	15%	>24	22
HPMC (K4M)	20%	17	11
	40%	>24	20
HPC (HXF Pharm)	40%	—	16
HPC (MF Pharm)	20%	1	0.5
	40%	5	0.75
Eudragit NE30D	1.8%	—	1
	3.2%	>24	

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Computer aided DLVO-based optimization of controlled flocculation in suspensions

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The properties of colloidal particles depend upon, or are affected by, the presence of a charge on the surface of the particles. Colloidal particles dispersed in liquid media may become charged mainly from selective adsorption of a certain charge. The acquired charge density localized in the plane of the surface of particles will create a difference in electrical potential between the charged surface rigidly held by the particles and the ions in the bulk of surrounding liquid, known as electrokinetic or *zeta* potential. This potential has practical application in the stability of colloidal dispersed systems, since this potential governs the degree of repulsion between adjacent similarly charged particles. DLVO theory of colloidal stability, developed in the 1940s, considers the electrostatic repulsion and van der Waals forces of attraction as a quantitative approach of the stability of hydrophilic suspensions. According to this theory, the repulsion and attraction forces result in potential energies of repulsion, V_R, and attraction, V_A, between the particles giving the total potential energy of interaction, V_T. In this investigation, the thermodynamic features of flocculation in suspensions stabilized with electrolytes have been studied. The aim of this study was to design a computer program, capable of predicting the optimum conditions for the production of stable flocculated suspensions, and to compare the theoretical results with those obtained experimentally. This program was used for calculating both V_A and V_R and plotting V_T against the distance of separation in each specific condition. The distance of separation, first and secondary zeta potentials and their corresponding electrolyte concentrations and valences were used to calculate the diameter of the Stern layer and it's potential. The range of electrolyte concentration and the distance of separation were then determined and divided into specific intervals. For a given electrolyte concentration, an iterative method of calculation was employed to give attraction energy for each specific distance. The values of repulsion energy for thick and thin electrical double layer were then calculated. Summation of repulsion and attraction energies gives a total potential energy for a given distance of separation. Finally, a DLVO curve was drawn for any predetermined electrolyte concentration and this procedure was continued until a satisfactory curve from the viewpoint of the height of barrier and depth of the primary minimum was obtained, predicting the optimized conditions for controlled flocculation.